The potential antiarrhythmic properties of sacubitril/valsartan: a case report

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The potential antiarrhythmic properties of sacubitril/valsartan: a case report

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Heart failure is a progressive disease in which heart pump dysfunction (heart failure with reduced ejection fraction, HFrEF) or elevated left ventricular (LV) filling pressures (heart failure with preserved ejection fraction) cause a syndrome clinically represented by symptoms and signs like breathlessness, fatigue, orthopnea, ankle swelling, elevated jugular venous pressure, third heart sound, pulmonary crackles.

Heart failure can be due to several causes such as myocardial ischemia, valvular disease and abnormal heart rhythms. Identifying the triggering causes is remarkably important, not only for therapeutic strategies, but also for the patient's prognosis. Evidence-based therapies [such as beta-blockers, angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), implantable cardioverter-difibrillator (ICD)/cardiac resynchronization therapy (CRT)] – which have been shown to reduce morbidity and mortality – are available only for HFrEF patients.[1]

Last but not least, a novel drug has been recently approved for HFrEF patients who are still symptomatic, namely sacubitril/valsartan, a combination of an angiotensin receptor blocker and a neprilysin inhibitor (which interferes with the degradation of natriuretic peptides and with the bradykinin system), finally resulting in an enhanced natriuresis, reduced vasoconstriction, myocardial relaxation and an antiremodeling effect.

The trial that led to its approval is PARADIGM – heart failure.[2]

In the course of this trial, treatment with sacubitril/valsartan proved to reduce mortality, hospitalizations and patients' symptoms. As is known, an important cause of death among patients with HFrEF is sudden arrhythmic death: despite only 16% of the study population having an ICD, a reduction in mortality due to cardiovascular death occurred anyway.

The patient is a 67-year-old male.

His clinical history is relevant for ischemic heart disease, due to a previous anterior ST-elevation myocardial infarction treated with coronary artery bypass graft (1992) in particular the left internal mammary artery, to bypass the left anterior descending artery.[3–5]

In 2006, the patient also had ICD implantation for primary prevention in severely reduced ejection fraction (30%).[6]

Despite the optimal medical therapy on top of the treatment (candesartan 8 mg/o.d., carvedilol 25 mg/b.i.d., canrenone 25 mg/o.d., amiodarone 200 mg/o.d. and ivabradine 7.5 mg/b.i.d.), and improvement of ejection fraction to 40%, during the last year several supraventricular tachycardia and a few nonsustained ventricular tachycardias (NSVT) were registered by the device, and by ICD home monitoring.

Some of the supraventricular tachycardias had a 1 : 1 conduction, with an erroneous recognition and ATP treatment by ICD.[7]

In particular, at the beginning of 2017 he had NSVT, so, in March, during an outpatient ICD control, carvedilol was titrated up to 25 mg/b.i.d.

From March to June 2017, the patient had 16 tachyarrhythmias – 5 of which were very fast potential life-threatening ventricular arrhythmias, which were treated successfully by the ICD with ATP – whereas 11 were supraventricular tachycardias, with 1 : 1 ventricular conduction, which ICD erroneously recognized as ventricular tachycardias. At this point, amiodarone 200 mg/die was introduced, but with poor success.

Indeed, in July 2017, the patient had 20 tachyarrhythmias, in particular supraventricular tachycardias with 1 : 1 ventricular conduction, which the ICD erroneously recognized as ventricular fibrillation and treated incorrectly (two of them with ATP); ivabradine 7.5 mg/b.i.d. was therefore introduced.

The patient's ICD home monitoring showed that, from July to September 2017, there were five other NSVTs, four of them potential life-threatening ventricular

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arrhythmias treated with ATP (refer to the figure in Annex: Boston report on arrhythmias).

Due to frequent arrhythmias his ejection fraction decreased to 35%. So, after a coronarographic control (September 2017) that showed the absence of new coronary lesions, the patient underwent an upgrade to atrioventricular node modulation and upgrade to cardiac resynchronization therapy defibrillators (CRT-D) (October 2017), despite a narrow QRS (<120 ms).

Despite this treatment, he was still symptomatic for dyspnea, so sacubitril/valsartan treatment was started 4 months later (February 2018), the ejection fraction still at 35%. After 3 months of treatment, an improvement in the symptoms and a significant reduction in both supraventricular and ventricular tachyarrhythmias were observed, while ejection fraction raised to 38%. At the last CRT-D control (January 2018) the device registered only two short runs of atrial flutter and no ventricular arrhythmias, with a 100% biventricular pacing.

European Society of Cardiology guidelines on the treatment of heart failure recently introduced sacubitril/valsartan for the treatment of HFrEF in those patients who, despite an optimal medical therapy (ACEis/ARBs, beta-blockers, MRAs, ICD), are still symptomatic.

The therapeutic effects of sacubitril/valsartan were underlined by the PARADIGM-HF trial, which showed how mortality is reduced in patients treated with this drug. An analysis of the trial population showed that only a low percentage of patients were ICD carriers (16%), although – despite this – there was a significant 20% reduction in sudden cardiac death.

Starting from this assumption, we cannot fail to include our patient in this setting.

Our case deals with a patient with a history of severe LV dysfunction, due to ischemic heart disease and concomitant arrhythmic problems (atrial fibrillation, potential life-threatening ventricular arrhythmias), the latter being persistent, despite the maximum dosage of antiarrhythmic therapy (amiodarone, carvedilol and ivabradine).[8] In addition, the patient was still symptomatic for dyspnea and he had also been hospitalized for heart failure, due to a recurrent supraventricular tachycardia inappropriately treated with the ICD intervention; sacubitril/valsartan was therefore introduced, and after 3 months a significant reduction in both supraventricular and ventricular arrhythmias was registered, despite nothing having been changed in his antiarrhythmic therapy. The only exception was the upgrading to CRT-D, which could prevent ventricular arrhythmias by biventricular pacing and reverse remodeling. The latter is not our case, since CRT was implanted not to resynchronize the ventricles (being QRS narrow), but to avoid desynchronization by continuous right ventricular pacing. Consequently, his ejection fraction did not change after 4 months of CRT therapy. However, we acknowledge that biventricular pacing could contribute to ventricular arrhythmias reduction.

The things we noted in this patient we had observed in a larger set of patients with overlapping features. A recent trial by de Diego *et al.*[9] collected data from 120 patients with ICD and severe LV dysfunction (ejection fraction <40%) being treated with optimal medical therapy and sacubitril/valsartan. Patients were followed for 9 months, with analyses of the arrhythmic events and ICD intervention therapies. The authors found that adding sacubitril/valsartan to the standard optimal medical therapy for heart failure significantly reduce nonsustained ventricular tachycardia, sustained ventricular tachycardia and appropriate ICD shocks; there was also an increase in biventricular pacing, due to a reduction in premature ventricular contraction (PVC)/h. In the course of this trial, supraventricular tachyarrhythmias – including the incidence of atrial fibrillation and the consequent inappropriate intervention of the ICD – were also reduced, although without reaching any statistical significance.

From our experience, and from the aforementioned trial, we can deduce that sacubitril/valsartan could have antiarrhythmic properties. Also the deremodeling effect of the drug can contribute to the reduction of the arrhythmic burden: in our patient ejection fraction raised from 35 to 38% thanks to the new drug. Future studies are needed to better investigate this issue.

Some possible mechanisms to explain this finding could be the following:

(1) The blockage of natriuretic peptides (NPs) degradation is by itself an important predictor of ventricular tachycardias and ICD shocks; NPs can also decrease the sympathetic activity (trigger for tachyarrhythmias), much more that enalapril alone can do.[10–12]
(2) The natriuretic effect of sacubitril/valsartan allows the diuretic dosage to be reduced, with a lower risk of hypokalemia, which in turn is responsible for ventricular tachycardias.[13]
(3) Sacubitril/valsartan could have reverse remodeling properties which lead to LV ejection fraction improvement.
(4) Sacubitril/valsartan-induced natriuresis reduces the volume overload causing myocardial stretch, which in turn is a trigger of PVC and ventricular tachycardia.[14,15]
(5) Reducing PVC also increases biventricular pacing, which improves the cardiac function.[16]
(6) A repetitive myocardial stretch can induce fibrosis and electrophysiological remodeling, a triggering element for the occurrence and persistence of arrhythmias.[17,18]

Even if the reduction in tachyarrhythmias, due to sacubitril/valsartan, is an enticing option, we should not

ignore that in the PARADIGM-HF study there was no difference between the two groups, with regard to the onset of atrial fibrillation.

We think that the putative antiarrhythmic properties of sacubitril/valsartan should be studied in greater detail, using patients on optimal medical therapies, including antiarrhythmic drugs and implantable devices that can be controlled in an outpatient setting or remotely.

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Conflicts of interest

M.M. has received consulting honoraria from Bayer, Novartis, Servier, Relypsa and Stealth Therapeutics. The other authors report no relationships.

References

1 Ponikowski P, Voors AA, Anker SD, *et al.* 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**:891–975.

2 McMurray JJ, Packer M, Desai AS, *et al.*, Investigators P-H and Committees. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**:993–1004.

3 Hillis LD, Smith PK, Anderson JL, *et al.* 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011; **124**:e652–e735.

4 Windecker S, Kolh P, Alfonso F, *et al.*, Authors/Task Force Members. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; **35**:2541–2619.

5 Ibanez B, James S, Agewall S, *et al.*, ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; **39**:119–177.

6 Wilkoff BL, Fauchier L, Stiles MK, *et al.* 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. *Europace* 2016; **18**:159–183.

7 Desai H, Aronow WS, Ahn C, *et al.* Incidence of appropriate cardioverter-defibrillator shocks and mortality in patients with heart failure treated with combined cardiac resynchronization plus implantable cardioverterdefibrillator therapy versus implantable cardioverter-defibrillator therapy. *J Cardiovasc Pharmacol Ther* 2010; **15**:37–40.

8 Kirchhof P, Benussi S, Kotecha D, *et al.* 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016; **18**:1609–1678.

9 de Diego C, González-Torres L, Núñez JM, *et al.* Effects of angiotensin–neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. *Heart Rhythm* 2018; **15**:395–402.

10 Hubers SA, Brown NJ. Combined angiotensin receptor antagonism and neprilysin inhibition. *Circulation* 2016; **133**:1115–1124; 5.

11 Levine YC, Rosenberg MA, Mittleman M, *et al.* B-type natriuretic peptide is a major predictor of ventricular tachyarrhythmias. *Heart Rhythm* 2014; **11**:1109–1116.

12 Vrtovec B, Delgado R, Zewail A, *et al.* Prolonged QTc interval and high B-type natriuretic peptide levels together predict mortality in patients with advanced heart failure. *Circulation* 2003; **107**:1764–1769.

13 Podrid PJ. Potassium and ventricular arrhythmias. *Am J Cardiol* 1990; **65**:33E–44E; discussion 52E.

14 Wang Z, Taylor LK, Denney WD, *et al.* Initiation of ventricular extrasystoles by myocardial stretch in chronically dilated and failing canine left ventricle. *Circulation* 1994; **90**:2022–2031.

15 Trayanova NA, Constantino J, Gurev V. Models of stretch-activated ventricular arrhythmias. *J Electrocardiol* 2010; **43**:479–485.

16 Gasparini M, Galimberti P, Ceriotti C. The importance of increased percentage of biventricular pacing to improve clinical outcomes in patients receiving cardiac resynchronization therapy. *Curr Opin Cardiol* 2013; **28**:50–54.

17 Von Lueder TG, Wang BH, Kompa AR, *et al.* Angiotensin receptor neprilysin inhibitor LCZ696 attenuates cardiac remodeling and dysfunction after myocardial infarction by reducing cardiac fibrosis and hypertrophy. *Circ Heart Fail* 2015; **8**:71–78.

18 Iborra-Egea O, Galvez-Monton C, Roura S, *et al.* Mechanisms of action of sacubitril/valsartan on cardiac remodeling: a systems biology approach. *NPJ Syst Biol Appl* 2017; **3**:12.